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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,280	09/30/2003	Timothy R. Billiar	14022-011001	7071

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

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10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/676,280	BILLIAR, TIMOTHY	
	Examiner	Art Unit	
	Blessing M. Fubara	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *4-9 and 15-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/06/07, 9/14/07, 2/2807*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt of IDS filed 2/28/07, 9/06/07 and 9/14/07. Examiner acknowledges remarks, request for extension of time and request for reconsideration filed 7/22/07. Claims 1-54 are pending. No claim is amended at this time.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3 and 10-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain specific concentration of CO effective to treat hemorrhagic shock, does not reasonably provide enablement for all concentration CO effective to treat hemorrhagic shock. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is scope of enablement.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient number of the factors are discussed below for a *prima facie* case.

1) Nature of the invention

The nature of the invention is the administration of carbon monoxide to a patient in order to treat hemorrhagic shock.

2) State of the prior art

Carbon monoxide (CO) is known in the art to be toxic to humans causing exhaustion and headache at levels of as low as 70 ppm (Omaye, "Metabolic modulation of carbon monoxide toxicity," in Toxicology 180 (2002) 139-150). The instant specification at paragraph [0040] talks about using Co at levels of 10 ppm to 3000 ppm for the treatment of hemorrhagic shock.

3) The predictability or lack thereof in the art

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific guidance is required to enable the artisan to practice the full scope of the claimed invention.

In the instant case, the scope of the claimed invention spans all concentrations of CO for effectively treating hemorrhagic shock. Also while the instant disclosure at paragraph [0040] envisions the use of 10-3000 ppm CO for inhalation, the prior art describes CO to be toxic at levels of as low as 70 ppm.

4) Amount of direction and guidance present

The direction and guidance provided is limited to amounts described in paragraph [0040] and not to all possible amounts. The listing of the amounts of CO at paragraph [0040] is an invitation to experiment because (see 5 below).

5) The presence or absence of working Examples

The working examples fail to provide any amount of CO useable in the invention, and by implication then refers back to the amounts disclosed in paragraph [0040]. The working examples do not correlate with the scope of the claims.

6) Quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine what concentration of CO to use that would not provide toxicity since applicants envision concentrations of 10-3000 ppm and Omaye discloses that CO levels of 70 ppm is toxic ands the claims is open ended to any amount of CO.

Therefore, in view of the Wands factors, and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in undue experimentation to test and use the scope of the claimed invention encompassed in instant claims, with no assurance of success.

This rejection can be overcome by the concentrations of CO effective for claimed method.

Response to Arguments

3. Applicant's arguments filed 7/11/07 have been fully considered but they are not persuasive.

A) Applicant states that the interview summary by Examiner Eyler indicating the issues raised in applications 10/053,535, 10/367,277, 10/600,182, 10/177,930, 11/401,722, 10/413,817, 10/371,666, and 10/455,564 during the interview with applicant's representatives, Janis K. Fraser and Todd E. Garcia should have included application 10/676,280.

B) Applicant states that because the current application 10/676,280 does not cite Mayr, Ryter, Dolinay or Choi as raising any enablement issues, or "opine that there is any reason to doubt that CO can be efficacious in human therapy," the examiner for the 10/676,280 is urged to acknowledge "for the record" that the scope of enablement issues raised in the interview summary for 10/439,632 will not be applied against the claims of 10/676,280.

C) Applicant vigorously asserts that the claims are in full compliance with the enablement requirement; that the potential toxicity of CO and side effects that may be experienced by an "individual" is irrelevant to the United States patent law, the fact that Omaye describes side effects experienced by persons exposed to varying "levels of CO does not legally support a proposition that practitioners would have been unable to use their skill in this instance to perform the presently claimed methods," so that the experimentation required of the practitioner to practice the invention is not undue.

D) Applicant argues that *in re Fisher* does not impose extraordinary stringent standard as the office is requiring, and applicant insists that so long as the disclosure contains sufficient information, persons of ordinary skill would be able to use the invention without undue experimentation.

E) Applicant states that the invention administers potentially toxic pharmaceutical gas to treat a disorder and that applicant demonstrated that 250 ppm CO inhaled can be used to prevent multiple organ failure in a rodent model, that the specification teaches how to make and deliver CO compositions and dosage amounts are discussed throughout the specification. That exhibit D prescribes treatment for 3 hours.

F) Applicant states that treatment regimen has to be adjusted to account for certain variables such as type of patient, size, age and conditions of the patient and that the skilled practitioner would not have reasons to doubt that the claimed methods would work despite the potential need for routine adjustments.

G) Applicant says that the state of the prior art recognizes that exposure of 200 ppm of CO for 1 hour produced "no noticeable effects," and that the point is that the art is well aware of what doses of CO could be tolerated for what periods of time without dangerous toxic effects. That nitric oxide, NO, a toxic gas has been approved for pharmaceutical use by the FDA.

H) Applicant states that the level of skill in the CO art is high at the time the invention was filed, that NO, which is more reactive than CO has been approved by the FDA for use and real potential toxicity of the NO has not "proven to be a barrier to widespread, successful use of the NO-based therapy ...."

I) Applicant argues that the skilled artisan in drug development and medicine routinely perform studies to determine effective doses and that the office has presented no evidence that determination of effective amounts of CO in humans, say, would be any less routine.

Response:

Regarding A), the point of fact is that application 10/676,280 was not included and it is speculative to assume what Examiner Eyler said or did not say. The interview summary stands for itself and there is no evidence on the record that application 10/676,280 was a subject for the interview of 21 February 2007 as shown below:

Applicants representatives Todd Garcia and Janis Fraser contacted the USPTO concerning consistency of enablement rejections in related applications 10/053535, 10/413817, 10/439832, 10/367277, 10/600182, 10/177930, 11/401722, 10/371666, 10/455564. It was conveyed that the Office's position at this time, based on the specific claim language in the relevant applications, is that the references Mayr et al. (Am. J. Resp. and Critical Care Medicine, Vol. 171, p. 354-360, 2005), Ryter et al. (Current Op. in Pharma. Vol. 6, p. 257-262, 2006), Dolinay et al. (In Breath Analysis, p 203-236), and Choi et al. (Am J. Resp. and Critical Care Medicine, Vol. 171, p1318-1319, 2005) raise a significant question of scope of enablement for treatment of human conditions and reduction of inflammation in humans based on unpredictability of rodent models for the human system. Serial numbers 10/053535, 10413817, 10/439832, 10/371666, and 10/455564 either have or will have actions with the enablement rejection set forth, based on the current claim language in said cases. The enablement rejection will not be applied to claims drawn to administering CO to organ donors, which claims are present in serial numbers 10/600182, 10/177930, and 11/401722..

Regarding B), the examiner would like to state that statement or record for any case proceeds independently and proceeds based on the facts in that case. The references applicant wants this examiner to disclaim, that is, Mayr, Ryter, Dolinay and Choi are not of record in this application 10/676,280 and making judgments and according relevance or irrelevance on those references at this time would be premature in the examination of this application since each statement or record proceeds independently based on the facts presented in that case at any stage in the examination process.

Regarding C), it is noted that while issues of toxicity and side effects are not within the jurisdiction of the Patent Office but that of the FDA, the outstanding issue is the scope of the enabling disclosure relative to the scope of the claims and when the full scope of what is claimed is analyzed based on what is enabled, the question is as follows as stated in the MPEP at 2164.08 [R-2] as follows in relevant sections:

"The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims."

"The specification must teach those skilled in the art how to make and use the **full scope of the claimed invention without undue experimentation**."

"As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims."

Now, claim 1 is seeking protection for all and every amount of CO to be administered to a subject having hemorrhagic shock. The specification envisions specific concentrations for treating hemorrhagic shock. The protection sought by the claim is broader than what is enabled by the disclosure. The Omaye reference is a negative teaching and raises the issue of what levels of CO is enabled. The PTO does not have laboratories.

Regarding D), it is brought to applicant's attention as was stated in the office action of 1/12/07, no amounts are claimed and because artisan has to determine what works and what does not

work, the experimentation is undue and the claims are seeking protection that is not commensurate with the enabling disclosure

Regarding E), the scope of the amount of CO to be administered is broader that the 250 ppm argued for by the applicant in the remarks. The claims have no recitation of 250 ppm. The invention is the claim and the claims do not recite any amount. Applicant's reference to certain amounts of CO in the specification supports the finding that the scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims. By arguing for limitations that are not in the claims but in the specification, applicant is attempting to import limitations from the specification into the claims. What is shown in exhibit D is not in the claims.

Regarding F), it is noted that applicant's argument supports the finding that the scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims. By arguing for limitations that are not in the claims but in the specification, applicant is attempting to import limitations from the specification into the claims.

Regarding G), It is noted that no amounts of CO is claimed and protection sought by the claimed invention is broader than the 200 ppm and the conditions of administration that applicant argues for. The scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims. The PTO is not the FDA and the examined claims are directed to the use of CO in whatever amounts to treat hemorrhagic

shock. The invention is not to the administration of NO to save lives and it would appear that NO is administered at specified levels/concentrations.

Regarding H), the claimed invention is not directed to the use of NO and the PTO is not the FDA. The scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

Regarding I), applicant appears to be suggesting that the effective dose of CO ought to be routinely determined by the skilled artisan while applicant is seeking protection for the claimed invention to use any amount of CO to treat HS and by requiring or assuming the skilled artisan to determine levels of CO based on circumstances around the subject, supports the finding that scope of enablement provided to one of skill in the art by the disclosure is not commensurate with the scope of protection sought by the claims.

The finding of lack of commensurate **scope of enablement** is maintained.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-3 and 10-14 are rejected under 35 U.S.C. 102(b) as being anticipate by Fujita et al. ("Paradoxical rescue from ischemic lung injury by inhaled carbon monoxide driven by depression fibrinolysis," Nature Medicine, 7, 598-604, 2001).

Bar-Or et al. (US 2005/0215468) describes ischemia as hemorrhagic shock in a more generalized sense.

Fujita discloses that inhaled CO protects against ischemic lung tissue injury (see the whole document). Inhalation meets claim 3 and 14. The lung tissue injury meets claims 1 and 12.

6. Claims 1-3 and 10-14 are rejected under 35 U.S.C. 102(e) as being anticipated by Pinsky et al. (US 2005/0048133 A1).

Pinsky treats tissues damaged (paragraph [0099], [0164]) by ischemic disorders (paragraph [0017]) with carbon monoxide inhalation (paragraphs [0028]-[0030], [0049], [0055], [0061], [0062]).

Response to Arguments

7. Applicant's arguments filed 7/11/2007 have been fully considered but they are not persuasive.

Applicant argues that:

a) the mice in Fujita did not suffer from hemorrhagic shock and that Bar-Or cannot be taken as evidence that ischemia of any sort elsewhere in the art denotes hemorrhagic shock.

b) Pinsky is concerned with ischemia and does not treat hemorrhagic shock and as such Pinsky does not anticipate the claims.

Response:

a) Claim 1 treats hemorrhagic shock in a patient and Bar-Or is a prior art that describes ischemia as hemorrhagic shock and applicant's argument does not negate the teaching of Bar-Or.

b) While Pinksy does not specifically state hemorrhagic shock, applicant admits that Pinsky is involved with ischemia and ischemia as per the teaching of Bar-Or is hemorrhagic shock.

No claim is allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Blessing M. Fubara whose telephone number is (571) 272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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